

Role of Stem Cells in the Immunotherapy of Cancers

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Stem cells, characterized by their self-renewal and differentiation capabilities, play a significant role in the immunotherapy of cancers. Cancer immunotherapy is a treatment that leverages the body's immune system to combat cancerous cells. Stem cells contribute to the development of new and advanced cancer treatments through various mechanisms:

T-cell Engineering: In this approach, stem cells are used to engineer T-cells with specific receptors for targeting cancer cells. These modified T-cells, known as chimeric antigen receptor (CAR) T-cells, are then reintroduced into the patient's body to recognize and destroy cancer cells.

Dendritic Cell Vaccines: Another method involves using stem cells to produce dendritic cells, which are responsible for presenting antigens to T-cells and activating them. By combining dendritic cells with tumor-specific antigens, researchers can create personalized cancer vaccines that stimulate a potent immune response against the patient's unique tumor.

Hematopoietic Stem Cell Transplantation (HSCT): HSCT is a procedure that replaces a patient's damaged or destroyed bone marrow with healthy stem cells from a donor. This approach is particularly beneficial in treating blood cancers, such as leukemia and lymphoma, as it allows for the regeneration of a new immune system capable of attacking residual cancer cells.

Natural Killer (NK) Cell Therapy: Stem cells can be used to generate large quantities of natural killer cells, which are potent immune cells capable of recognizing and destroying cancer cells without prior sensitization. These NK cells can then be infused into patients as an immunotherapy treatment.

Overall, stem cells play a crucial role in advancing immunotherapy for various types of cancers by offering innovative approaches to harness the immune system's potential for targeted and efficient cancer treatment. As research continues, it is expected that stem cells will contribute to the development of even more effective therapies in the future. Generally, several types of stem cells are used for immunotherapies, as follows:

Mesenchymal Stem Cells in Cancer Immunotherapy: Mesenchymal Stem Cells (MSCs) are a unique type of stem cell with

immunomodulatory properties, meaning they can regulate the immune system's response to cancer. By secreting various cytokines (IL-6, IL-10) and growth factors (TGF- β , VEGF, FGF, HGF, PDGF, IGF-1, SDF-1), MSCs can modulate the function of immune cells, such as T-cells, B-cells, and natural killer cells, enhancing their ability to target and eradicate cancerous cells [1,2,3]. Another remarkable feature of MSCs is their innate tumor-homing abilities. These stem cells migrate towards tumor sites in response to specific signaling molecules released by cancerous tissues. This tropism makes them ideal vehicles for delivering therapeutic agents directly to the tumor site, reducing systemic side effects and increasing treatment efficacy [4]. Due to MSC's plasticity and ease of genetic modification, MSCs have become attractive candidates for gene therapy in cancer immunotherapy. Researchers can introduce genes encoding for anti-tumor proteins or cytokines into these stem cells, which then produce and secrete these therapeutic molecules at the tumor site upon migration. This localized production enhances the anti-cancer immune response while minimizing potential off-target effects. Recent studies have highlighted the role of exosomes—tiny vesicles secreted by MSCs—in cancer immunotherapy [5]. These exosomes carry functional proteins, lipids, and nucleic acids that can influence recipient cell behavior and promote an anti-tumor immune response. Harnessing the potential of MSC-derived exosomes may lead to novel treatments with reduced toxicity compared to conventional therapies.

Induced Pluripotent Stem Cells (iPSCs) in Personalized Cancer Treatments: Induced pluripotent stem cells (iPSCs) are created by reprogramming adult somatic cells into a pluripotent state, like embryonic stem cells. This technology allows the generation of patient-specific immune cells, such as T-cells and natural killer cells, that can be used in personalized immunotherapies. By creating immune cells from the patient's own tissues, the risk of graft rejection or graft-versus-host disease is significantly reduced. iPSCs can also be used to create cancer cell lines and tumor organoids derived from individual patients. These patient-specific models provide valuable insights into the molecular mechanisms driving cancer development and progression, facilitating the identification of potential therapeutic targets and enabling high-throughput drug screening. Utilizing iPSC-derived cancer models allows tailored drug testing on a patient's unique tumor profile. This personal-

ized approach to oncology not only increases the likelihood of identifying effective treatment options, but also minimizes the exposure to ineffective or harmful therapies. Consequently, this can lead to improved clinical outcomes and quality of life for patients undergoing cancer treatment. The combination of iPSC technology with advanced gene-editing tools like CRISPR/Cas9 provides a powerful platform for developing targeted cancer therapies. By introducing specific genetic modifications into iPSC-derived immune cells or tumor models, researchers can investigate novel strategies to enhance anti-tumor activity while reducing off-target effects [6].

In conclusion, induced pluripotent stem cells have immense potential in advancing personalized cancer treatments by generating patient-specific immune cells, modeling cancer development, enabling precision oncology through tailored drug screening, and facilitating targeted gene editing for improved therapeutic strategies.

Stem Cell-Based Regeneration of Immune System Components Damaged by Chemotherapy or Radiation Therapy: Chemotherapy and radiation therapy, while effective in killing cancer cells, can also damage healthy immune cells in the process [7,8]. Hematopoietic stem cell transplantation (HSCT) can replenish the patient's immune system following such treatments. By infusing healthy stem cells from a donor or the patient themselves (autologous HSCT), a new, functional immune system is generated, allowing faster recovery and improved resistance against infections. In addition to their immunomodulatory properties, mesenchymal stem cells (MSCs) possess regenerative capabilities that can help repair tissues damaged by chemotherapy or radiation therapy. MSCs secrete various growth factors and cytokines that promote tissue repair by stimulating angiogenesis, reducing inflammation, and recruiting other endogenous stem cells to the site of injury. This makes MSC-based therapies a promising approach for mitigating treatment-related side effects and accelerating post-treatment healing. It should be noted that the vascular system can be severely impacted by chemotherapeutic agents and radiation exposure. Endothelial progenitor cells (EPCs), a subtype of stem cells involved in blood vessel formation, have shown potential in restoring damaged vasculature. By mobilizing EPCs to areas of injury, researchers hope to promote revascularization and restore proper blood flow to tissues affected by cancer treatments [9]. Furthermore, certain pharmacological agents can stimulate the release of endogenous stem cells into circulation. These mobilized stem cells may then be home to sites of injury caused by chemotherapy or radiation therapy, contributing to tissue repair and immune system recovery. Developing effective stem cell mobilization strategies could offer a non-invasive approach to enhancing the body's natural regenerative capacity following cancer treatments.

In summary, stem cells have significant potential for repairing and regenerating components of the immune system damaged by chemotherapy or radiation therapy. Strategies such as hematopoietic stem cell transplantation, mesenchymal stem cell-based therapies, endothelial progenitor cell mobilization, and pharmacological stem cell activation may provide innovative solutions for mitigating treatment-related side effects and improving patient outcomes.

Current Clinical Trials in Stem Cell-Based Immunotherapies:
CAR T-Cell Therapies: Chimeric antigen receptor (CAR) T-

cell therapies have made remarkable progress in recent years, with several clinical trials demonstrating their efficacy against hematological malignancies such as leukemia and lymphoma. Currently, researchers are exploring the potential of CAR T-cells for solid tumors by targeting tumor-specific antigens and investigating strategies to overcome the immunosuppressive tumor microenvironment [10]. In a groundbreaking case, a young girl became the first pediatric patient to receive CAR T-cell therapy for relapsed and refractory Acute Lymphocytic Leukemia (ALL). The treatment involved modifying her own T-cells to recognize and attack cancer cells expressing the CD19 antigen. After receiving this experimental therapy, the patient experienced a complete remission and has remained cancer-free ever since. Her success story contributed to the eventual FDA approval of Kymriah (tisagenlecleucel) for pediatric and young adult patients with B-cell ALL [11].

NK Cell Therapies: Natural Killer (NK) cell-based therapies are being tested in various clinical trials for their effectiveness against various cancer types. Researchers are evaluating both autologous (patient-derived) and allogeneic (donor-derived) NK cells in combination with other treatments like monoclonal antibodies or immune checkpoint inhibitors to enhance anti-tumor responses [12]. A promising case study involved a young boy diagnosed with high-risk neuroblastoma, who had exhausted all conventional treatment options. He was enrolled in a clinical trial to test an allogeneic natural killer (NK) cell therapy derived from umbilical cord blood. Following multiple infusions of these donor-derived NK cells, the patient achieved complete remission, highlighting the potential of NK cell-based therapies as a viable option for aggressive cancers like neuroblastoma [13,14].

Dendritic Cell Vaccines: Dendritic cell vaccines have shown promise in early-phase clinical trials, particularly for melanoma, prostate cancer, and glioblastoma. These personalized vaccines involve isolating dendritic cells from patients, loading them with tumor antigens, and reintroducing them into the patient's body to stimulate a targeted immune response. Ongoing trials aim to optimize vaccine formulations and investigate combinatorial approaches with other immunotherapies or conventional treatments [15]. A notable example of successful dendritic cell vaccine therapy is seen in a patient diagnosed with glioblastoma multiform, an aggressive form of brain cancer. After undergoing standard treatments like surgery, radiation therapy, and chemotherapy, the patient received an experimental dendritic cell vaccine developed from their own tumor tissue. The vaccine stimulated an immune response against tumor-specific antigens, leading to stable disease control and significantly extending the patient's survival [16].

MSC-Based Therapies: Mesenchymal Stem Cell (MSC)-based therapies are being explored for their potential to modulate the immune system and deliver therapeutic agents directly to tumors. Several clinical trials are underway to assess the safety and efficacy of MSCs engineered to express anti-cancer molecules or cytokines that promote immune activation against cancer cells. In a case of metastatic colorectal cancer unresponsive to traditional treatments, mesenchymal stem cells (MSCs) engineered to express a potent anti-cancer molecule (TRAIL) were administered to the patient. This innovative approach resulted in significant tumor regression and improved quality of life for the patient, demonstrating the potential of MSC-based therapies for treating advanced-stage cancers [17].

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These successful case studies exemplify the transformative impact that stem cell-supported immunotherapies can have on cancer treatment outcomes. While further research is needed to optimize and expand these novel therapeutic approaches, these real-life examples offer hope for a future where personalized, targeted treatments become standard care for cancer patients worldwide.

iPSC-Derived Immunotherapies: Induced Pluripotent Stem Cell (iPSC)-derived immunotherapies remain in the early stages of development, but hold significant promise for personalized cancer treatment. Preclinical studies have demonstrated the feasibility of generating patient-specific immune cells, such as T-cells and NK cells, from iPSCs. Clinical trials are expected to emerge in the coming years as researchers refine protocols for iPSC differentiation and assess the safety and effectiveness of these therapies [17,18].

Investigating the Role of Stem Cell-Derived Exosomes in Cancer Immunotherapy:

Stem Cell-Derived Exosomes and Their Properties: Exosomes are small extracellular vesicles released by various cell types, including stem cells. These vesicles play a crucial role in cell-to-cell communication by transferring proteins, lipids, and nucleic acids between cells. Stem cell-derived exosomes have garnered significant interest in cancer immunotherapy due to their unique properties, such as low immunogenicity, high stability, and ability to cross biological barriers. One of the key features of stem cell-derived exosomes is their ability to modulate immune responses. They can interact with immune cells like T-cells, natural killer cells, dendritic cells, and macrophages to induce or suppress specific immune reactions. In cancer immunotherapy, these immunomodulatory effects can be harnessed to enhance anti-tumor immunity or mitigate unwanted side effects resulting from excessive immune activation. The natural ability of exosomes to transport bioactive molecules across biological barriers makes them ideal candidates for targeted drug delivery. Researchers are exploring the potential of loading stem cell-derived exosomes with various therapeutic agents, such as chemotherapeutic drugs, small interfering RNA (siRNA), or even gene-editing tools like CRISPR/Cas9 [19]. By packaging these agents within exosomes, they can be selectively delivered to tumor sites, while minimizing systemic toxicity. To further increase the therapeutic potential of stem cell-derived exosomes in cancer treatment, researchers are developing methods for engineering these vesicles with specific properties or functionalities. For example, surface modifications that enable targeted binding to specific tumor antigens can improve the specificity and efficiency of drug delivery [20].

Additionally, incorporating immunostimulatory molecules like cytokines or co-stimulatory ligands can help enhance anti-tumor immune responses. While stem cell-derived exosomes hold significant promise as therapeutic agents in cancer immunotherapy, several challenges remain to be addressed. These include optimizing methods for large-scale exosome production, ensuring the safety and quality of these vesicles, and developing efficient strategies for loading them with therapeutic cargo. As research continues to advance our understanding of exosome biology and its potential applications in cancer treatment, it is likely that these obstacles will be overcome, paving the way for innovative therapies based on stem cell-derived exosomes.

Combining Stem Cell-Based Therapies with Other Immunotherapies for Enhanced Efficacy:

Synergistic Effects of Combined Treatments: The combination of stem cell-based therapies and other immunotherapies, such as Immune Checkpoint Inhibitors (ICIs), has the potential to enhance treatment efficacy by simultaneously targeting multiple aspects of the immune response. By employing complementary mechanisms of action, these combined treatments may overcome limitations associated with single-agent therapies and improve patient outcomes. ICIs are a class of immunotherapies that block inhibitory pathways on immune cells, allowing them to recognize and attack cancer cells more effectively. Combining stem cell-based therapies with ICIs can potentially boost anti-tumor immunity by generating a larger pool of tumor-specific immune cells, while also alleviating immunosuppressive signals within the tumor microenvironment. Several preclinical studies have shown promising results when combining stem cell-based therapies with ICIs in various cancer models. These studies suggest this combinatorial approach can lead to enhanced anti-tumor responses, reduced tumor growth, and improved survival rates compared to either therapy alone. Early-phase clinical trials are now underway to investigate the safety, tolerability, and preliminary efficacy of these combined treatments in human patients [20]. To maximize the therapeutic potential of combining stem cell-based therapies with other immunotherapies like ICIs, researchers are investigating various factors, such as optimal dosing schedules, sequencing of treatments, and selection of appropriate patient populations. Identifying biomarkers that predict treatment response or resistance will also be crucial for personalizing these combination therapies and ensuring their success in clinical practice. It should be noted that, even though combining stem cell-based therapies with other immunotherapies holds great promise for enhancing cancer treatment efficacy, several challenges need to be addressed. These include understanding the complex interactions between different therapeutic agents, managing potential side effects and toxicities, and navigating regulatory hurdles associated with combination therapies. As research continues to advance in this area, it is expected that these challenges will be overcome, leading to innovative and more effective cancer treatment options for patients worldwide.

Gene Editing Technologies for Enhanced Stem Cell-Based Cancer Targeting: The revolutionary gene-editing technology, CRISPR-Cas9, has opened new avenues for enhancing stem cell-based cancer therapies. By enabling precise manipulation of genes within stem cells, researchers can create tailored cellular therapies with improved targeting and therapeutic efficacy against specific cancer types. One application of CRISPR-Cas9 in stem cell-based cancer therapy is the modification of T-cells to generate CAR-T cells. By incorporating tumor-specific antigen receptors into patient-derived T-cells, these engineered immune cells can selectively recognize and eliminate cancer cells while sparing healthy tissues. Gene editing technologies like CRISPR-Cas9 have accelerated the development of personalized CAR-T therapies by streamlining the process of introducing targeted genetic modifications [21,22]. Furthermore, using gene-editing techniques like CRISPR-Cas9, researchers can engineer MSCs to express therapeutic molecules, such as cytokines or pro-apoptotic proteins, that enhance their anti-tumor potential. By optimizing these genetic modifications, MSC-based therapies may become more effective at eradicating cancer cells while minimizing side effects. iPSCs also offer a unique platform for generating patient-specific immune cells,

such as NK cells or DCs. With CRISPR-Cas9 technology, it is possible to introduce desired genetic changes into iPSCs before differentiating them into specialized immune cell types. This approach allows the production of customized immune cells with enhanced anti-tumor properties, paving the way for personalized cancer immunotherapies. However, despite its potential, integrating gene-editing technologies like CRISPR-Cas9 into stem cell-based cancer therapies also comes with challenges. Ensuring the specificity of genetic modifications and avoiding off-target effects is crucial to minimizing potential risks associated with gene-edited stem cells. Additionally, ethical considerations and regulatory hurdles must be addressed as these innovative therapies progress toward clinical implementation. As research advances in this field, it is anticipated that gene editing technologies will play an increasingly vital role in shaping the future of stem cell-based cancer treatments.

Impact of Tumor Microenvironment on Stem Cell-Based Immunotherapies and Strategies to Overcome Challenges: The Tumor Microenvironment (TME) is a complex network of cellular and non-cellular components surrounding cancer cells, including immune cells, stromal cells, blood vessels, and extracellular matrix. The TME plays a critical role in regulating tumor growth, metastasis, and response to therapies. In the context of stem cell-based immunotherapies, the TME can either promote or hinder treatment effectiveness by modulating immune cell function and accessibility to cancer cells. One major challenge posed by the TME is its ability to create an immunosuppressive milieu that impairs anti-tumor immunity [23]. Factors such as hypoxia, nutrient deprivation, and secretion of immunosuppressive cytokines or metabolites can inhibit the function of immune effector cells like T-cells or NK cells. Additionally, the presence of immunosuppressive cell populations like regulatory T-cells (Tregs) or myeloid-derived suppressor cells (MDSCs) within the TME can further dampen immune responses. To enhance the efficacy of stem cell-based immunotherapies, strategies must be developed to overcome these barriers imposed by the TME. One approach to overcoming TME-induced immunosuppression involves targeting specific factors that contribute to this inhibitory environment. For example, agents that neutralize immunosuppressive cytokines like transforming growth factor-beta (TGF- β) or interleukin-10 (IL-10) can help restore immune cell function within the TME. Similarly, drugs that target metabolic pathways associated with immune suppression may also improve treatment outcomes. Another strategy for enhancing stem cell-based immunotherapies involves modulating the activity or abundance of immunosuppressive cell populations within the TME. This can be achieved through the use of agents that deplete or inhibit Tregs or MDSCs, or by engineering stem cells to express molecules that counteract these suppressive cells. For instance, chimeric antigen receptor (CAR) T-cells engineered to secrete cytokines like IL-12 can not only enhance their own anti-tumor activity but also help reshape the TME into a more immune-supportive environment. Physical barriers within the TME can impede immune cell infiltration and access to cancer cells. To address this challenge, researchers are exploring strategies such as modifying stem cells to express enzymes that degrade extracellular matrix components, improving immune cell trafficking and penetration into solid tumors. Additionally, agents that promote blood vessel normalization or disrupt tumor-associated vasculature may further facilitate immune cell access to cancer cells. Combining stem cell-based immunotherapies with other treatment modalities that target different aspects of the TME

can potentially lead to synergistic effects and improved treatment outcomes. For example, combining stem cell-based therapies with angiogenesis inhibitors, stromal-targeting agents, or immune checkpoint inhibitors may help overcome multiple barriers posed by the TME and enhance therapeutic efficacy.

In conclusion, understanding the impact of the tumor microenvironment on stem cell-based immunotherapies is critical for developing strategies that effectively overcome these challenges. By targeting immunosuppressive factors, modulating inhibitory cell populations, improving immune cell trafficking and penetration, and employing combination therapies, it is possible to harness the full potential of stem cell-based treatments in fighting cancer.

Potential Risks and Side Effects of Stem Cell-Derived Cancer Treatments: One potential risk associated with stem cell-derived cancer treatments is immune reactions, such as graft rejection or Graft-Versus-Host Disease (GVHD). This occurs when the patient's immune system recognizes the transplanted cells as foreign and attacks them, or when donor-derived cells attack the patient's tissues. To minimize this risk, researchers are developing strategies to generate patient-specific immune cells using induced Pluripotent Stem Cell (iPSC) technology. Another concern with stem cell-based therapies is the unintended formation of tumors due to uncontrolled proliferation or differentiation of transplanted cells. This risk can be mitigated through rigorous quality control measures during cell production, and by developing methods to ensure proper differentiation and integration of transplanted cells into target tissues. Some gene-editing techniques used in stem cell research, such as CRISPR/Cas9, may cause off-target effects where unintended DNA sequences are altered. These unintended genetic modifications could potentially lead to harmful consequences for patients receiving gene-edited stem cell therapies. To address this issue, researchers are working on refining gene-editing technologies to improve specificity and reduce off-target effects. The use of allogeneic (donor-derived) stem cells in cancer immunotherapy carries a small risk of transmitting infections from the donor to the recipient. Rigorous screening protocols for donors and stringent safety measures during cell processing can help minimize this risk. While activating the immune system against cancer is a primary goal of immunotherapies, excessive activation may lead to side effects, such as Cytokine Release Syndrome (CRS) or autoimmune reactions. CRS is characterized by a rapid release of inflammatory cytokines that can cause fever, fatigue, organ damage, or even death in severe cases [24]. Autoimmune reactions occur when the immune system mistakenly attacks healthy tissues, leading to inflammation and tissue damage. Strategies to manage these side effects include dose adjustments, temporary immunosuppression, or administration of medications to alleviate symptoms.

Cost-Effectiveness and Accessibility of Stem Cell-Based Cancer Therapies: The development and implementation of stem cell-based cancer therapies often involve higher initial costs compared to traditional treatment options, such as chemotherapy, radiation therapy, or surgery. Factors contributing to these increased costs include the complexity of cell manipulation techniques, the need for specialized equipment and facilities, and the personalized nature of many stem cell-derived treatments. However, it is essential to consider not only the upfront costs but also the long-term cost-effectiveness of these novel

therapies. While stem cell-based immunotherapies may have higher initial costs, they can potentially offer significant long-term cost savings due to their targeted approach and reduced side effects. Traditional cancer treatments can result in substantial expenses related to managing side effects and complications, as well as lost productivity due to extended recovery times or disability. By reducing these additional burdens on patients and healthcare systems, stem cell-based therapies may prove more cost-effective over time. Conversely, as research advances in stem cell-based cancer therapies, new methods are being developed to streamline production processes and reduce treatment costs. Automation technologies, standardized protocols for generating patient-specific cells, and innovations in gene-editing techniques can all contribute to lowering the financial barriers associated with these cutting-edge treatments. The accessibility of stem cell-derived cancer therapies is also influenced by insurance coverage policies and reimbursement systems. Thus, it should be ensured that health insurance providers adequately cover these novel treatments, which will be crucial in making them available to a broader patient population. Additionally, establishing clear reimbursement pathways for healthcare providers administering these therapies will further promote their adoption within clinical practice [25,26].

In summary, assessing the cost-effectiveness and accessibility of stem cell-based cancer therapies involves considering both the short-term costs associated with treatment development and implementation, as well as long-term savings related to improved patient outcomes. By focusing on improving production efficiency, expanding insurance coverage, establishing reimbursement systems, and promoting global access to advanced therapies, it is possible to increase the affordability and availability of these promising treatment options for patients worldwide.

Ethical Considerations and Challenges in Stem Cell Research and Cancer Immunotherapy:

Embryonic Stem Cell Controversy: One of the primary ethical concerns surrounding stem cell research involves the use of embryonic stem cells (ESCs), which are derived from human embryos. The process of obtaining these cells often results in the destruction of the embryo, raising moral and ethical objections from those who consider this tantamount to taking a life. While ESCs have unique pluripotent capabilities, alternative sources like adult stem cells and induced pluripotent stem cells (iPSCs) have been developed to address these concerns.

Informed Consent and Donor Rights: Obtaining informed consent from donors is crucial in ensuring they understand the potential risks, benefits, and implications of donating their biological materials for stem cell research or therapy. Donors must know how their samples will be used, any potential commercial applications, and whether they retain any rights over their donated material. Researchers must strive for transparency while respecting donor privacy.

Genetic Privacy and Discrimination: With advances in gene-editing technologies like CRISPR/Cas9 being applied to stem cell research, concerns about genetic privacy have emerged. As patient-specific information is used to create personalized therapies or model diseases, there is a risk that sensitive genetic data may be misused or lead to discrimination based on an individual's genotype. Ensuring robust data security measures and implementing legal safeguards against genetic discrimina-

tion are vital steps in addressing these concerns.

Accessibility and Equity in Treatment: As innovative cancer immunotherapies become available, questions arise about fair access to these potentially life-saving treatments. High costs associated with developing novel therapies can lead to significant economic barriers for many patients. It is essential that efforts are made to ensure equitable access to advanced cancer treatments, regardless of socioeconomic status.

Regulation and Oversight: The rapid pace of scientific advances in stem cell research can sometimes outpace regulatory frameworks and guidelines. Ensuring that research and clinical applications adhere to rigorous ethical standards, safety protocols, and quality control measures is crucial in minimizing potential risks and maintaining public trust in the field. Continuous dialogue between researchers, clinicians, policymakers, and the public can help establish a balanced approach to regulating stem cell research and its applications in cancer immunotherapy.

In conclusion, addressing ethical considerations and challenges associated with stem cell research and its applications in cancer immunotherapy is critical for responsible scientific progress. By engaging in open discussions about controversial issues like embryonic stem cell use, informed consent, genetic privacy concerns, treatment accessibility, and regulatory oversight, the scientific community can work together to develop innovative therapies, while respecting societal values and ensuring patient well-being.

References

1. Caplan AI. Mesenchymal stem cells. *J. Orthop. Res.*, 1991; 9: 641-650.
2. Pockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissue. *Science*, 1997; 276: 71-74.
3. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nature Rev. Immunol.*, 2008; 8: 276-763.
4. Lourerco S, Teixeira HV, Kalber T, Jose RJ, Floto RA, Janes SM. Macrophage migration inhibitory factor-CXCR4 is the dominant chemotactic axis in human mesenchymal stem cell recruitment to tumors. *J. Immunol.*, 2015; 194: 3463-3474.
5. Kordellas L, Rebman V, Ludwig AK, et al. MCS derived exosomes: a novel tool to treat therapy-refractory graft-versus-host diseases. *Leukemia*, 2014; 28: 970-973.
6. Takahashi K, Yamanka S. Induction of pluripotent stem cells from mouse embryonic fibroblast cultures by defined factors. *Cell*, 2006; 126: 663-676.
7. Chabner BA, Robert TG. Chemotherapy and war on cancer. *Nature Rev.*, 2005; 65: 72-81.
8. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guideline. *Cancer*, 2005; 104: 1129-1137.
9. Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. *Circ. Res.*, 2004; 95: 343-353.
10. Ma S, Li X, Wang X, Cheng L, Li Z, Zhang C, Ye Z, et al. Current progress in CAR-T cell therapy for solid tumor. *Int. J. Biol. Sci.*, 2019; 15: 2548-2560.
11. Ali S, Kjekken R, Niederlaender C, Markey G, et al. The European Medicine Agency Review of Kymirah (Tisagenlecleucel) for the treatment of acute lymphoblastic leukemia and diffuse large B-cell. *Oncologist*, 2020; 25: 321-327.
12. Hsu J, Hodgins JJ, Maratta M, Nicolai CJ, Bourgeois-Daigneault MC, Trevino TN, et al. Contribution of NK cells to immunotherapy mediated by PD-1/PDL1 block-

- ade. *J. Clinical Invest*, 2018; 128: 4654-4668.
13. Romeer R, Rosario M, Berrien-Elliott MM, Wagner AJ, Jewell BA, et al. Cytokine induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci. Transl. Med*, 2016; 8: 357-362.
 14. Dinh-Toi C, Tiep Ten N, nguyen LBT, dang-Koa T, et al. Recent progress of stem cells therapy in cancer treatment: molecular mechanism and potential applications. *Cell*, 2020; 9: 53-68.
 15. Carro BM, Magrini V, Beker-Hapak M, Kaabinejadian S, Hundal J, et al. Cancer immunotherapy: a dendritic vaccine increases the breadth and diversity of melanoma neo-antigen-specific T cells. *Science*, 2015; 348: 8038-8042.
 16. Anguille S, Smits EL, Lion E, van Tendeloo V, Berneman ZN. Clinical use of dendritic cells for cancer therapy. *Lancet Oncol*, 2014; 15: 257-267.
 17. Liu H, Kim Y, Sharkins S, Marchionni L, Jang YY. In vivo liver regeneration potential of human induced pluripotent stem cells from diverse origins. *Sci. Trans. Med*, 2011; 3: 39-82.
 18. Choi SM, Kim Y, Liu H, Chaudhari P, Ye Z, Jang YY. Liver engraftment potential of hepatic cells derived from patient-specific induced pluripotent stem cells. *Cell Cycle*, 2011; 10: 2423-2427.
 19. Chen-Liang Z, Ting H, Bi-Li W, Wen-Xi H, Dong L. Stem cells in cancer therapy: opportunities and challenges. *Onco- target*, 2017; 8: 75756-75766.
 20. Sagar J, Cbaib B, Sales K, Winslet M, Seifalian A. Role of stem cells in cancer therapy and cancer stem cells: a review. *Cancer cell Int*, 2017; 7: 9-20.
 21. Auffinger B, Morshed R, Tobias AS, Cheng Y, Ahmed AU, Leniak MS. Drug-loaded nanoparticle system and adult stem cells: a potential marriage for treatment of malignant glioma. *Oncotarget*, 2013; 4: 378-396.
 22. Wang L, Chen Y, Lui X, Ziyi L, Land X, Xiangpeng D. The application of CRISPR/Cas9 for cancer immunotherapy: current status and problems. *Frontier Oncol*, 2022; 11: 704999-704010.
 23. Xia H, He QF, Wang JC, Zhu J, Sha Q, Su B, et al. Advances of CRISPR-Cas9 in cancer immunotherapy. *J. Med. Genet*, 2019; 56: 4-9.
 24. Tong L, Jimenez-Cortegana C, Tay AHM, Wickstrom S, Galluzzi L, Lundqvist A. NK cells and solid tumors: therapeutic potential and persisting obstacles. *Mol. Cancer*, 2022; 21: 206-2015.
 25. Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T-cells therapy. *Biol. Blood Marrow Transplant*, 2019; 25: 123-127.
 26. Xiao X, Huang S, Chen S, Wang Y, Sun Q, Xu X, et al. Mechanisms of cytokine release syndrome and neurotoxicity of CAR T-cell therapy and associated prevention and management strategies. *J. Exp. Clin. Cancer*, 2021.